Office of Cellular, Tissue and Gene Therapies; an Overview

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Tragedy to Action

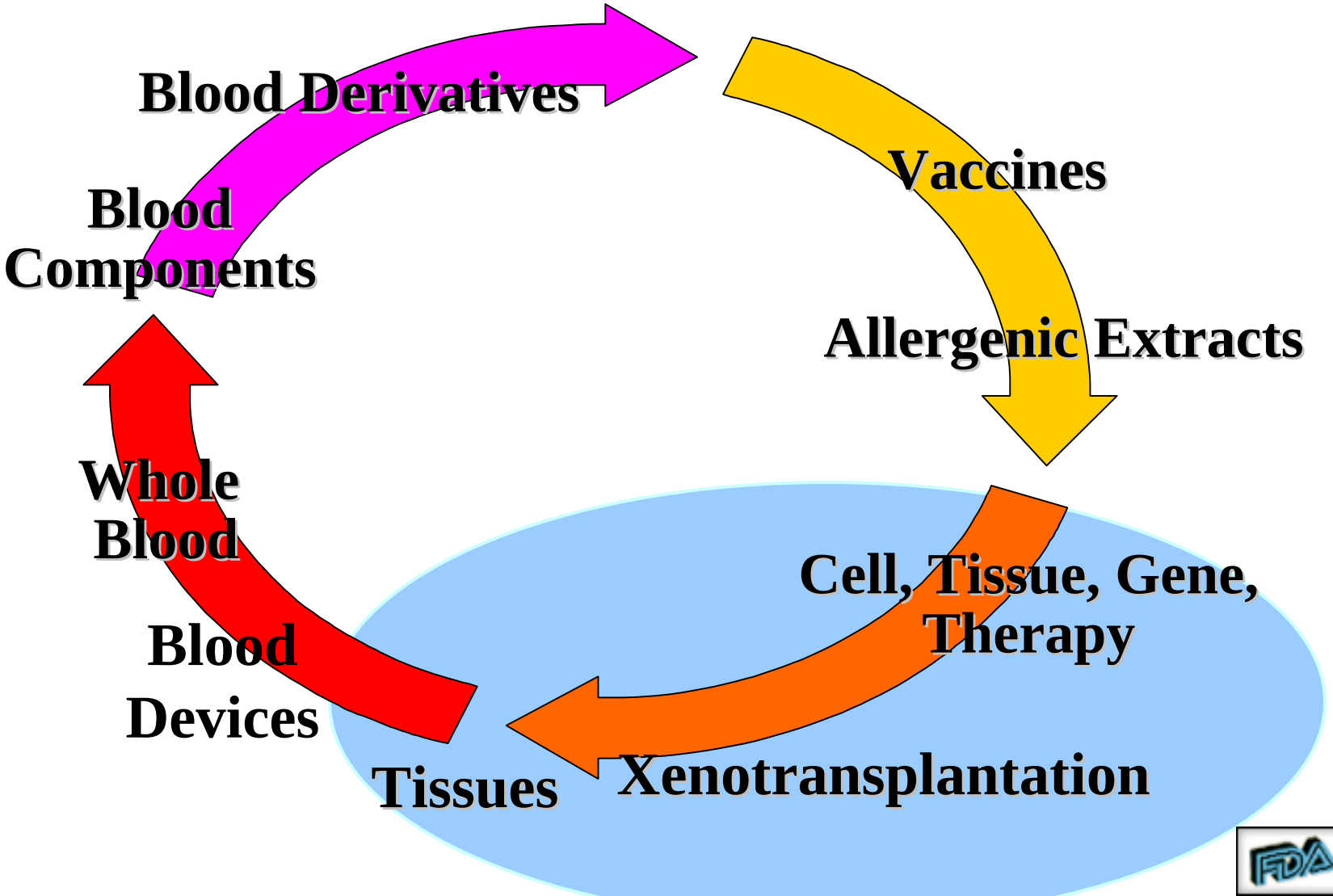
- 13 children in St. Louis died of tetanus after receiving diphtheria antitoxin (1901) from a horse named Jim
  - "This tragedy convinced Congress and the public that producing antitoxin or vaccine was not a simple matter like weighing out a dose of a drug on a scale."
    - Margaret Pittman, "The Regulation of Biological Products, 1902-1970"

Biologics Control Act of 1902

- **"Although the preventive and curative powers of viruses, serums, toxins, antitoxins, and analogous products has long since been established, certain unfortunate accidents, notably those which recently occurred in St. Louis, Mo., have tended to discredit their use.** ***The extreme value of the preparations in preventing and curing disease renders it of prime importance, therefore, that action be taken to preserve the confidence of the medical profession and of the community generally in them…"***

  - ***Legislative history of the Biologics Control Act, 1902***

BIOLOGICS PRODUCTS REGULATED BY CBER



Office of Cellular, Tissue and Gene Therapies: Mission

- Plan, develop and implement a comprehensive risk-based regulatory, problem solving framework for cellular, tissue and gene therapies
- Therapies to Repair, Replace, Restore, Regenerate normal body function
- Assure the safety, identity, purity, and potency of novel products
- Regulatory and review responsibilities:
  - Tissues
  - Cellular and Tissue-based products
  - Gene Therapies
  - Xenotransplantation
  - Unique assisted reproduction (ooplasm transfer)
  - Combination Products containing living cells/tissues

America's "secret" Renewable 40-year Bond

- in 1957: Sputnik
  - US Commitment to research, education
  - Expansion of the NIH, Medical specialties
  - DARPA, PARC, ATT, Silicon Valley
- 2000 and beyond
  - biotech, gene therapies, regeneration
  - personal computers, franchises, internet
    - Democratization of information
    - Accountability for actions
  - Human Genome Project, embryonic stem cells

“A promise made…

- **Prevent**
  - **Vaccines, the most cost effective improvement of the public health**
- **Replace**
  - **Blood, insulin, organ and tissue transplantation**
- **Treat**
  - **antibiotics, antihypertensives, antiinflammatories**

and to deliver…”

- to those untouched by “conventional” therapeutics
  - Genetic Diseases
  - Neurological/metabolic/degenerative diseases
    - Brittle diabetics
    - Parkinson’s, Alzheimer’s, ALS
  - Cardiovascular disease
  - Life altering diseases
    - Replace, repair
  - Patient Centered Therapies

A New Class of Product Requiring INDS

- **1993 FR Statement Somatic and Gene Therapies**
  - **"*Somatic cell therapy* is the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries in humans by the administration of autologous, allogeneic, or xenogeneic cells…**
  - **Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, … or other alteration of their biological characteristics."**

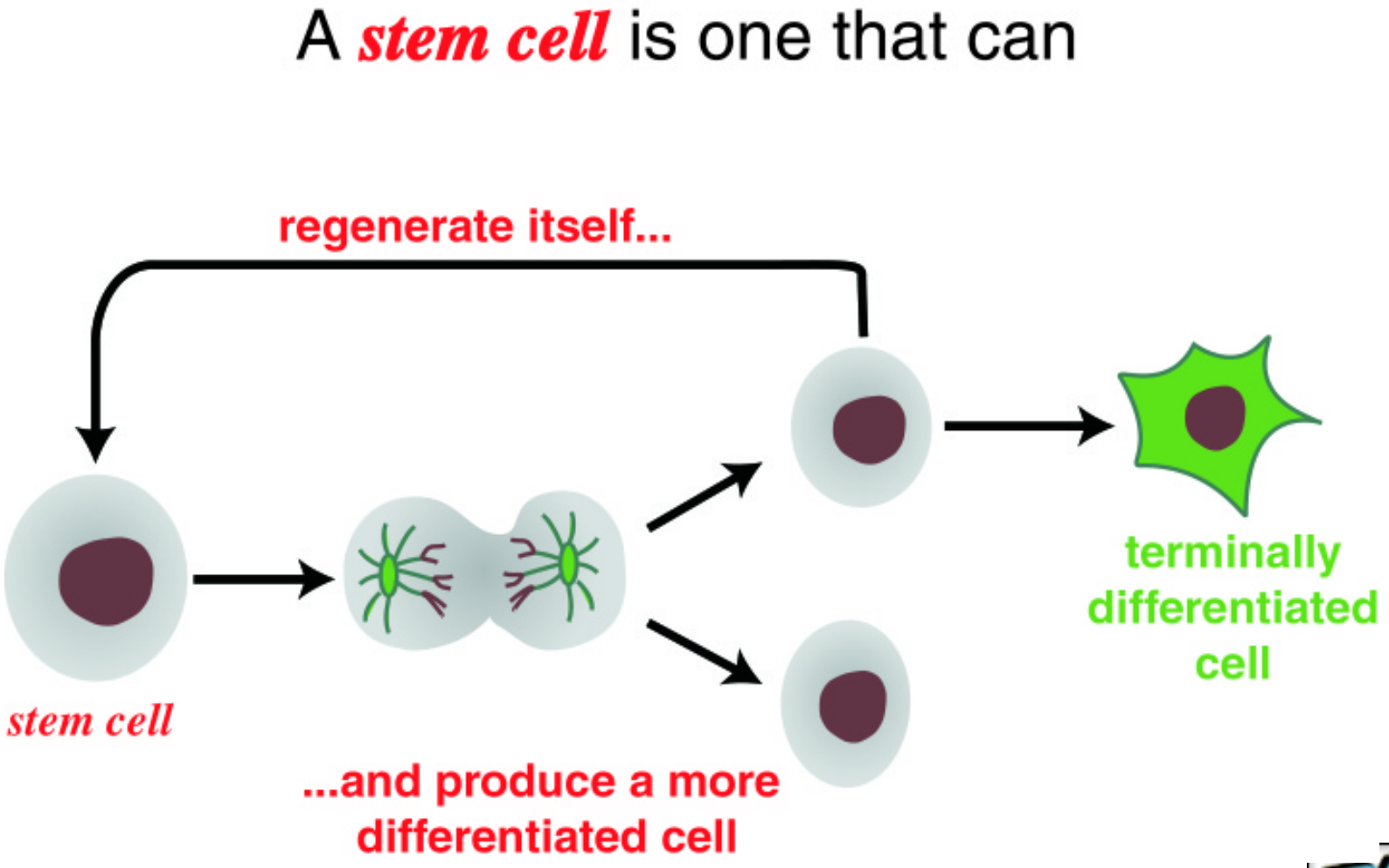
A New Class of Product (cont)…

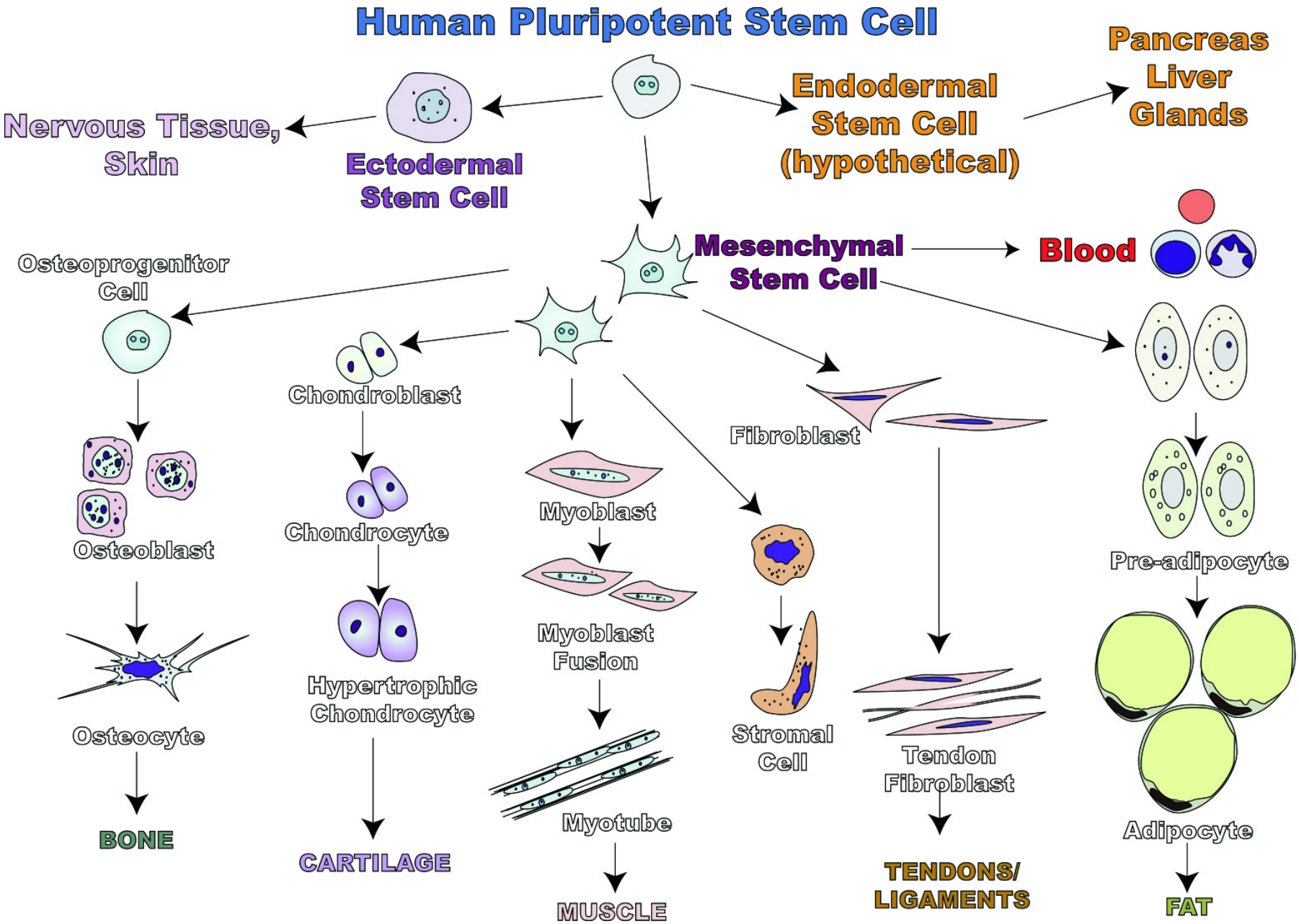
- **1993 FR Statement Somatic and Gene Therapies**
  - **"*Gene therapy* is a medical intervention based on modifications of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration or may be altered in vivo by gene therapy products given directly to the subject..."**

Implementation of Risk Based, Problem Solving Regulation

- Cellular, tissue and gene therapies evolve rapidly and present regulatory issues continually.
- Issues germane to this area are extraordinarily complex, multifaceted and subject to rapid change.
- It is not feasible to maintain specific staff experts on every product, procedure and clinical indication.
- Foster a cadre of experts in relevant disciplines, whose knowledge, skills and abilities enables them to stay current at a time of explosive development in the field, yet who are also experts in biological product regulation.
- Create and foster educational partnerships, internal reviewer guidance, clear expectations for industry and academia

Present and Future Complexity of Somatic Cell Therapies




Human Pluripotent Stem Cell
Nervous Tissue, Skin
Ectodermal Stem Cell
Endodermal Stem Cell (hypothetical)
Pancreas
Liver
Glands
Mesenchymal Stem Cell
Blood
Osteoprogenitor Cell
Osteoblast
Osteocyte
BONE
Chondroblast
Chondrocyte
Hypertrophic Chondrocyte
CARTILAGE
Myoblast
Myoblast Fusion
Myotube
MUSCLE
Stromal Cell
Fibroblast
Tendon Fibroblast
TENDONS/ LIGAMENTS
Pre-adipocyte
Adipocyte
FAT

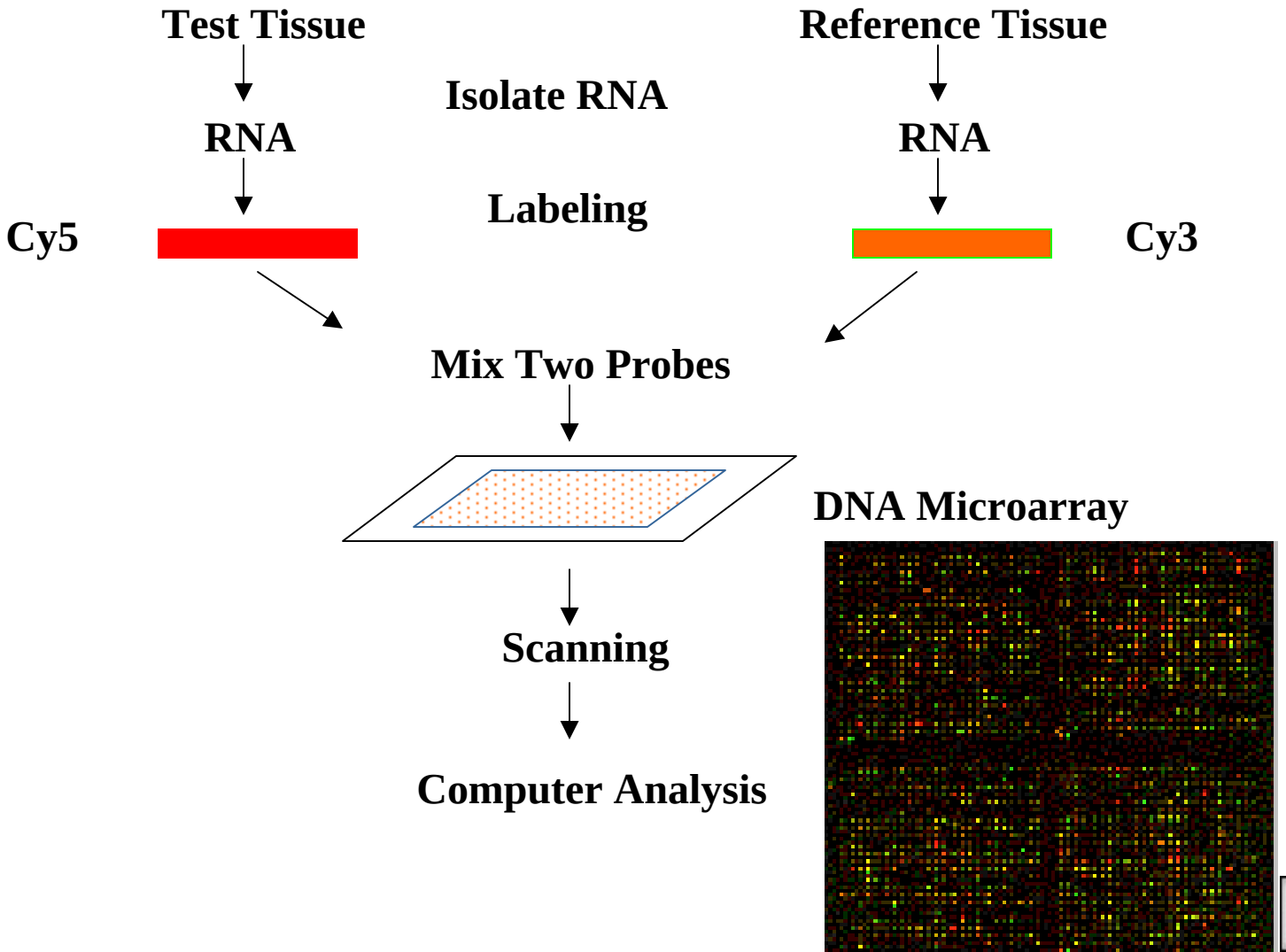
Steps to Encourage Product Development

- Experience with cellular therapies
- Guidance
  - Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) - 8/15/2003
- Interagency Agreement (IAG) National Institute of Neurologic Diseases and Stroke
- FDA meetings with stem cell providers

Gene Expression Profiles for Characterization of Cell Banks

- No easy methods for characterization
- Things to watch for in Cell Banks:
  - metabolic status: affects the yield
  - tumorigenicity: safety issue
  - Contamination with adventitious agents: safety issue
- Global gene expression profile may be useful to assess the status of a cell culture
- Identification of markers for cell bank consistency

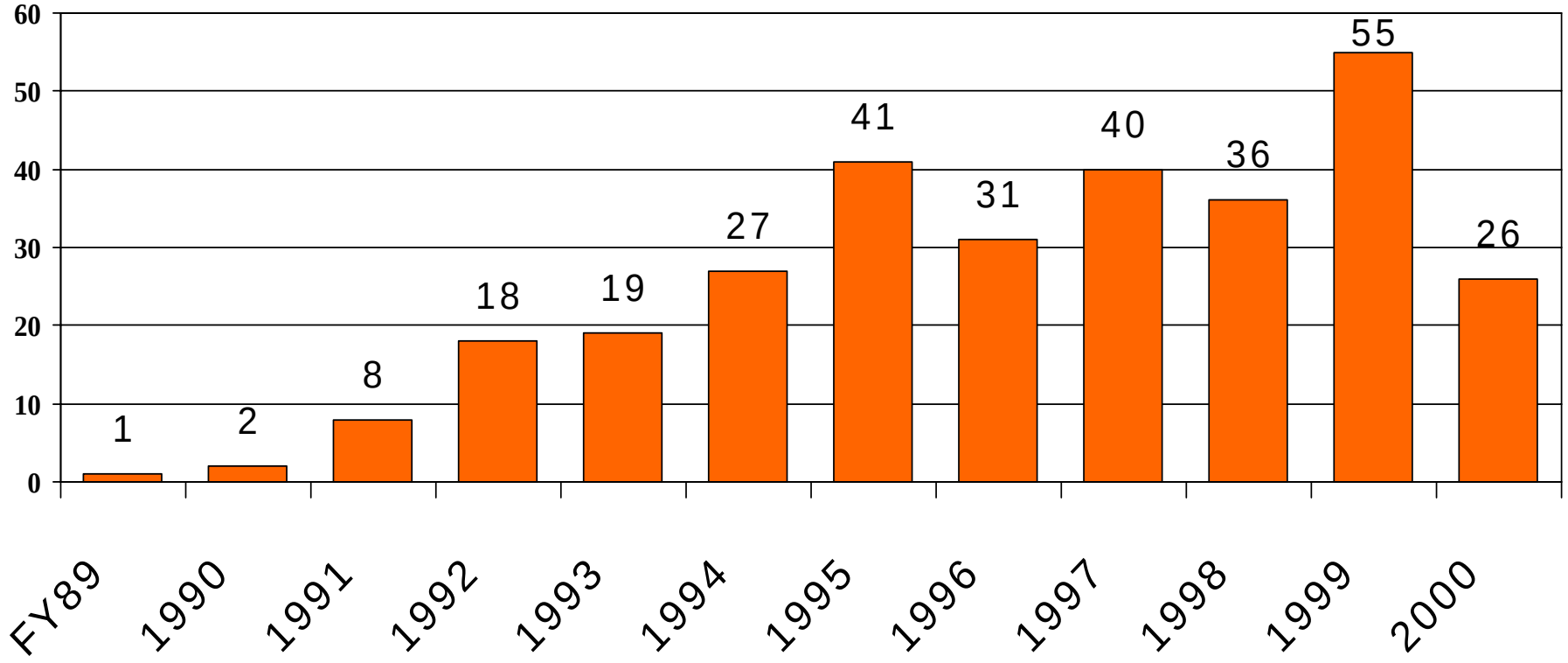
Gene Expression Analysis Using DNA Microarray



FDA-NIH-Industry-Academia Collaboration

- Bhattacharya, et al. Gene Expression in Human Embryonic Stem Cell Lines: Unique Molecular Signature. Blood, Dec 30, 2003; Blood First Edition
- 92 genes expressed in six huESC studied, including Nanog, GTCM-1, connexin 43 (GJA1), oct-4 and TDGF1 (cripto).
- 15 genes appear to be novel
- Useful for standards for huESC characterization

CBER Gene Therapy INDs Received FY 89-2000

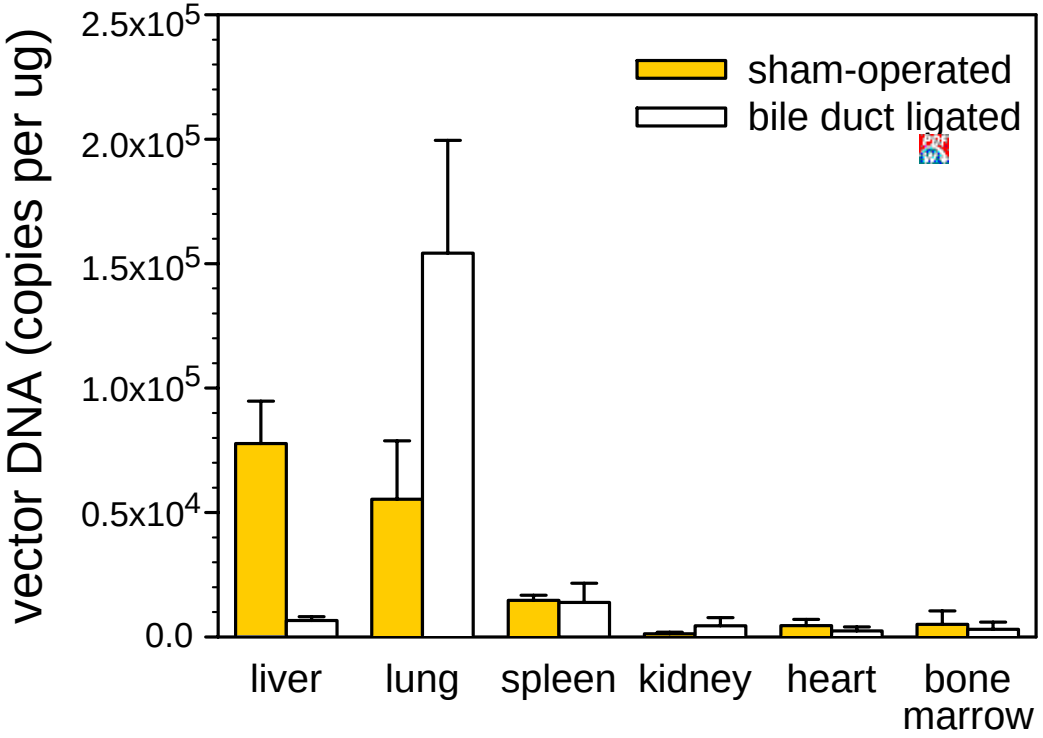


Issues and FDA Approaches

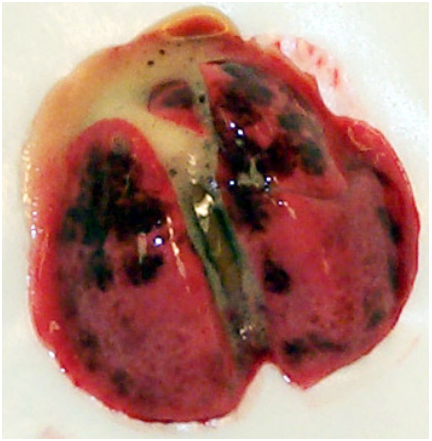
- Sept 1999: 18 year old died in gene therapy trial
  - BIMO inspections of 69 gene therapy clinical sites
  - Adenovirus Reference Material
    - Simek, S., Byrnes, A., and Bauer, S. FDA perspectives on the use of the adenovirus reference material. BioProcessing 1:40-42, 2002
  - New FDA Project
    - Smith, Tian, Muller and Byrnes. “Unexpected pulmonary uptake of adenovirus vectors in animals with chronic liver disease”. Gene Therapy (2004) 11, 431-438

Development of New Animal Model to Evaluate Adenovirus Toxicity

Physical biodistribution – quantitative PCR

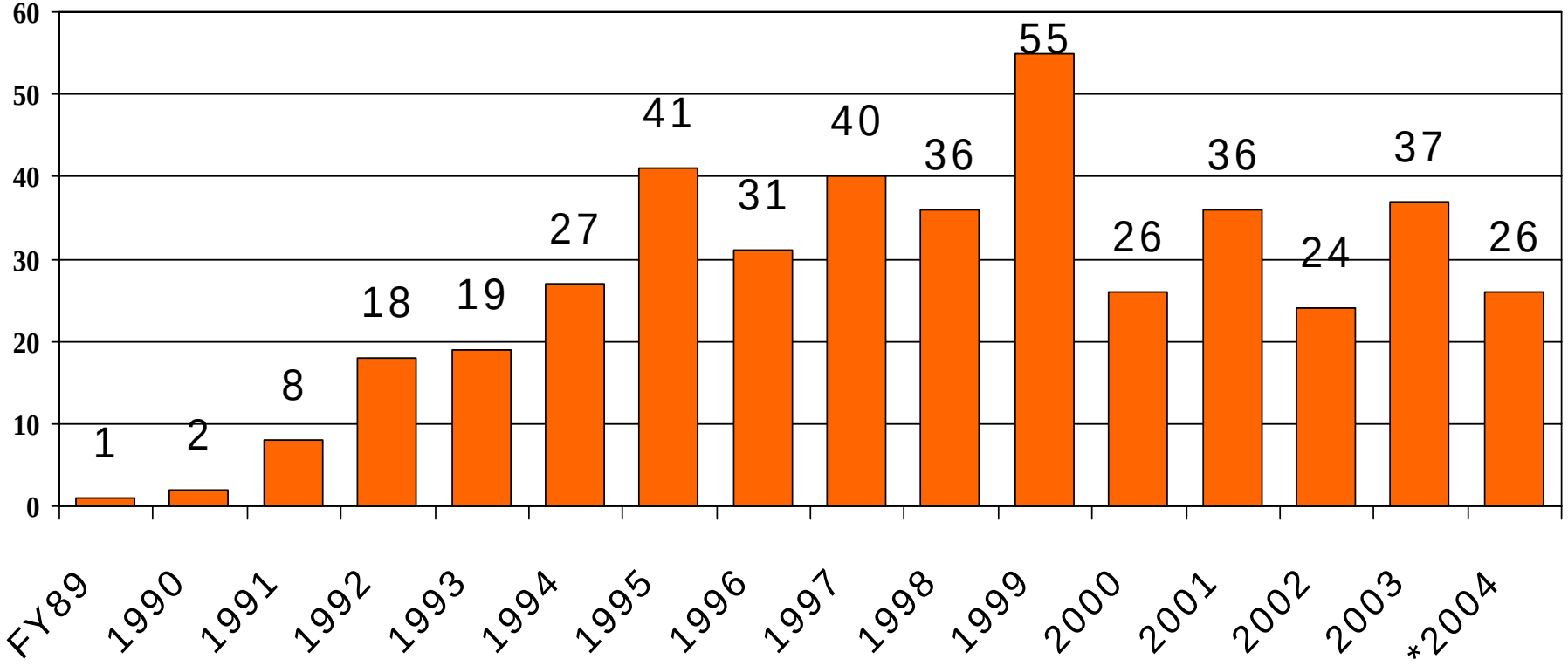


Pulmonary hemorrhage and edema in a cirrhotic rat given adenovirus vector



Andrew Byrnes

CBER Gene Therapy INDs Received FY 89-2004



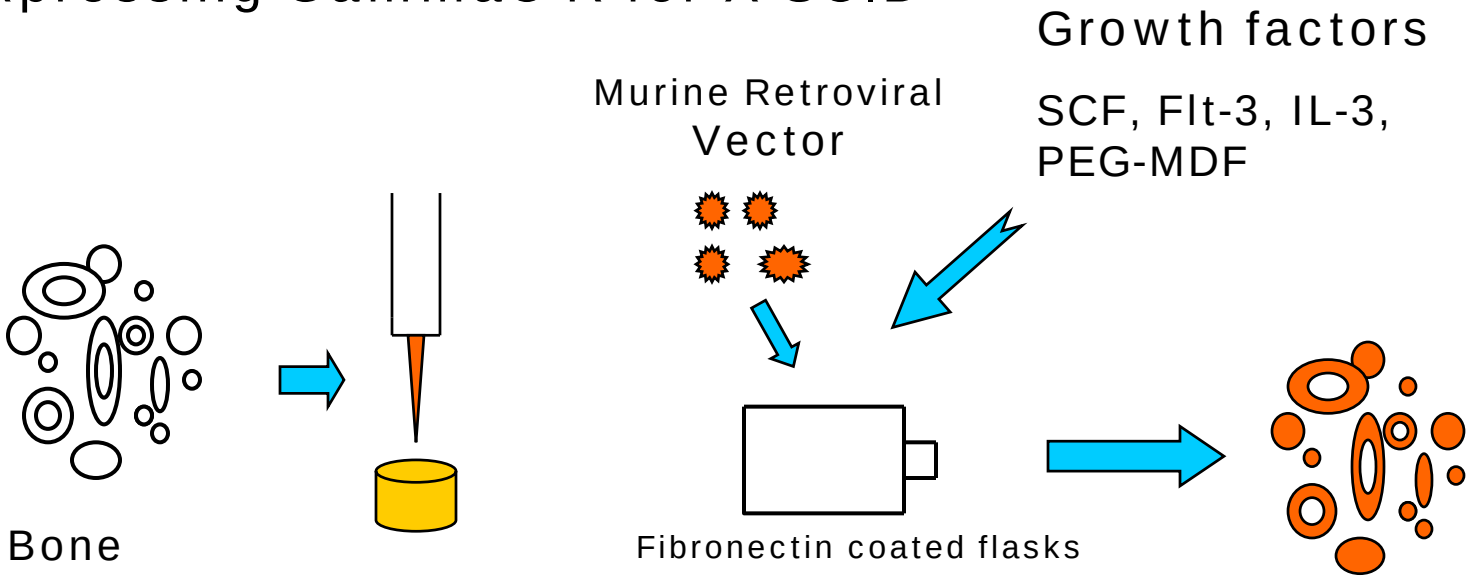
*FY2004 thru 4 March 2004

A Patient Centered Therapy

- **X-linked Severe Combined Immunodeficiency Syndrome (X-SCID)**
  - **Lack of gamma-c chain with consequent lack of cytokine receptors needed for T-cell function**
  - **Death within first year of life from severe recurrent infections**
  - **Transplant of HLA-identical marrow >90 % survival; haploidentical transplant 50-70 %**
  - **Survivors may still need gamma globulin, unknown long term survival**

Complexity of (a) Gene Therapy Product

Ex Vivo Transduced CD34+ Cells Expressing GammaC-R for X-SCID



Complexity continued…

- Cord Blood/Bone Marrow
  - Donor screening, adventitious agents, purity, potency
- Devices
  - Monoclonal antibodies, surface markers, extracellular matrix
- Retroviral Vectors
  - Cell substrates, adventitious agents, reversion to wild type
- Specified Products (SCF, Flt-3, etc)
  - Purity, potency, novel use (ancillary, not as primary effector)
- Cellular Product
  - Characterization, potency, evidence of gene transduction

Gene Therapy For X-SCID

- In France, 9/10 children showed evidence of immune reconstitution following gene therapy
- Late August 2002, one successfully treated child developed leukemia-like symptoms
- FDA Biologics Response Modifier Advisory Committee (BRMAC) reviewed case on 10 October 2002
- Consensus of BRMAC
  - Gene insertion gave both therapeutic effect and caused insertional mutagenesis
  - Because of potential superior immune reconstitution with gene therapy, studies should proceed with caution with stringent testing for clonal expansion of T-lymphocytes
  - Revision of informed consent process for ALL retroviral gene therapies

Gene Therapy For X-SCID (cont)

- Late December 2002, a second successfully treated child developed leukemia-like symptoms In France, with a similar insertion
- FDA Biologics Response Modifier Advisory Committee (BRMAC) reviewed case on 28 Feb 2003
- Consensus of BRMAC
  - Gene insertion at/near LMO-2 site caused insertional mutagenesis leading to leukemias
  - Now cannot be considered a random event
  - GT using HSC for X-SCID should not be primary therapy unless no alternative therapies

What Next?

- OCTGT/CBER-American Society of Gene Therapy (ASGT) Workshop on Non-Clinical Toxicology in Support of Licensure of Gene Therapies March 13-14, 2003 in Arlington, VA.
- ASGT Annual Meeting June 4-8, 2003 DC
  - Retrovirus Insertional Mutagenesis, C. Wilson, chair
  - Ethical and Policy Dilemmas in Clinical Gene Therapy Studies-Balancing Real Benefits and Real Risks
- Stem Cell Clonality and Genotoxicity Retreat, December 10, 2003, San Diego, CA
  - Updates on preclinical models
  - International perspective on clinical trials for SCID

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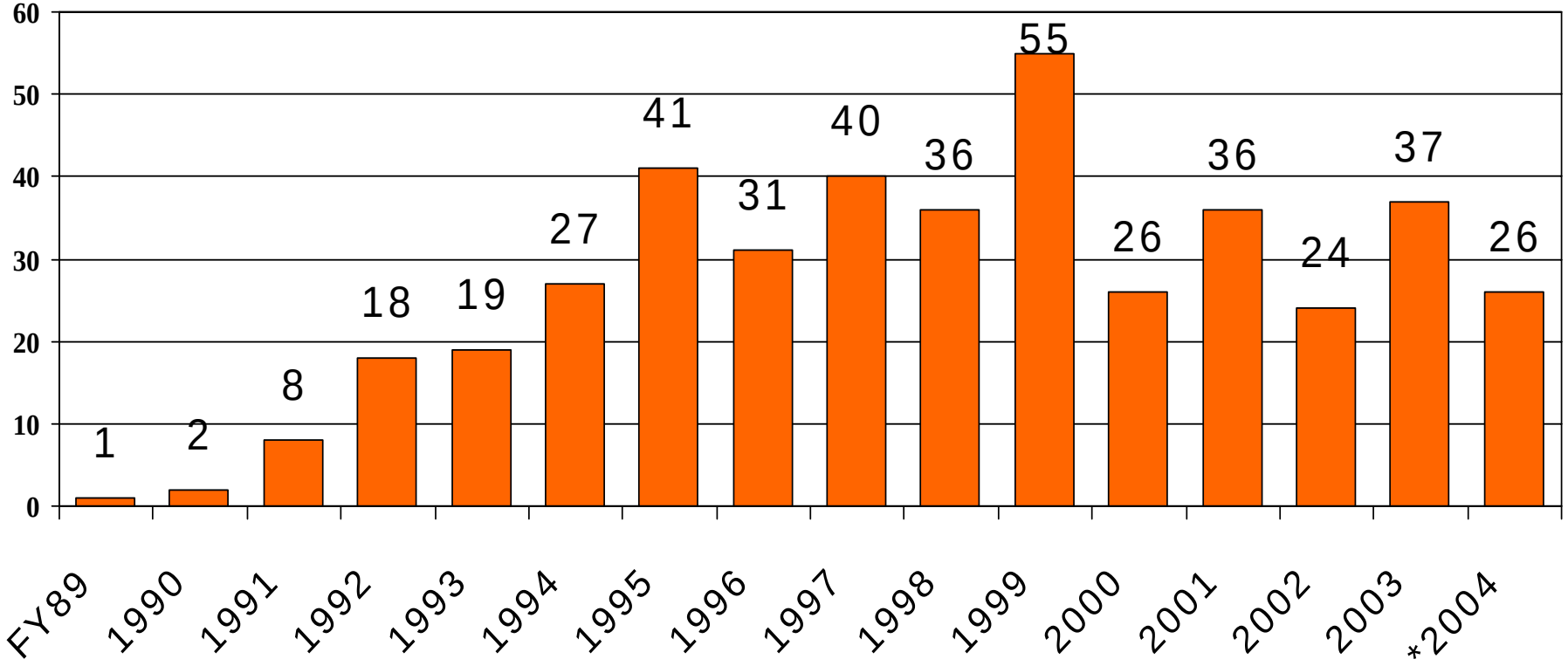
- FDA-NIH/OBA Gene Therapy Safety Conference in planning

CBER Gene Therapy INDs Received FY 89-2004



*FY2004 thru 4 March 2004

Duty for All

- "... *The extreme value of the preparations in preventing and curing disease renders it of prime importance, therefore, that action be taken to preserve the confidence of the medical profession and of the community generally in them…"*
  - *Legislative history of the Biologics Control Act, 1902*